Remarks

Reconsideration of this Application is respectfully requested.

Based upon the above Amendments and the following Remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Upon entry of the forgoing amendment, claims 1-4, 6-8, 10-11 and 13-38 are pending in the application, with claims 1, 24, 29, 31, 33, 34, 35 and 38 being the independent claims. Claims 1, 15, 24, 29, 31, 33, 34, 35 and 38 are sought to be amended. Claims 5, 9, 12 are sought to be canceled without prejudice or disclaimer, and Applicants reserve the right to prosecute these claims in a divisional application. Claim 38 has been withdrawn from consideration, but rejoinder to the remaining claims is respectfully requested upon allowance. These changes are believed to introduce no new matter, and their entry is respectfully requested. Support for the amendments is found throughout the applications and the originally filed claims.

Applicants wish to thank the Examiner for pointing out the allowability of Claim 15.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 1-4, 6-7, 10, 13 and 16-37 under 35 U.S.C. § 112, first paragraph, as being enabling only for compounds wherein U-V form a ring as disclosed on page 5, lines 7-10.

While Applicants respectfully disagree with the Examiner's assessment, the subject matter wherein U and V are independent has been canceled from the claims, leaving only compounds wherein U-V form a ring. Applicants cancel this subject matter without prejudice or disclaimer, in order to expedite prosecution, and reserve the right to prosecute the compounds wherein U and V are independent in a divisional application.

Therefore, this rejection is rendered moot, and Applicants respectfully request that the Examiner withdraw the rejection.

The Examiner rejected claims 1-4, 6-8, 13-14, 16-28 and 37 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

There is a relationship between the binding of the claimed compounds to the NMDA receptors and their pharmaceutical properties. The main usefulness of the claimed compounds is the relief of pain. Experiments have been performed to show the pain relieving effect of the claimed compounds.

The Examiner stated that the ability to bind to the NMDA receptor was not necessarily an accurate predictor of the usefulness of a compound as a drug, and that there was no clear correlation between *in vivo* potency of the compounds on NMDA receptor binding or functional assay and the *in vivo* measured analgesic activity. However, as shown by the formalin test data presented in Tables 1 and 2 set forth below, one of skill in the art would be able to predict the usefulness of the claimed compounds in the relief of pain. When evaluating these results, the *in vivo* measurement of analgesic effect was performed after oral administration of all compounds. Oral administration was intended to be used for pain relief; *e.g.*, neuropathic pain conditions. These drugs can best be used if they do exert their intended effect of pain relief after such oral administration. It has been shown that NMDA receptors are involved in formalin-induced pain behavior. This effect is at least partially mediated by spinal NMDA receptors. Thus, in order to exert an analgesic effect after oral administration, a compound must be absorbed from the gastrointestinal (GI) tract and reach the targeted sites of action; *i.e.*, the NMDA receptors in the central nervous system. Although the ability of the compounds to be absorbed from the GI tract may differ considerably depending upon the physicochemical properties of the compound, one can increase the activity of such a compound by altering the vehicle employed. For example, the absorption of poorly water soluble compounds can be considerably increased by using solubilizers for oral administration.

In addition, the metabolic stability of the compounds can also affect their *in vivo* efficacy. Intraperitoneal administration may result in higher absorption with some compound that are quickly metabolized or poorly absorbed from the GI tract. Accordingly, when the *in vitro* potent NMDA antagonist compounds that had a lower analgesic effect were administered by other routes or in different form, increased potency was detected. All of the reference compounds of the invention, with one exception, produced potent antinociceptive effect with approximately 5 mg/kg ED_{50} value. This

supports the notion that any compound having high potency for antagonizing NMDA receptors will produce a considerable analgesic effect in the formalin test according to their pharmacological features.

Table 1 (Formalin test)

ID	NMDA IC_{50} nM	ED_{50} Mg/kg p.o. in Tween Suspension	ED_{50} with Intraperitoneal (i.p.) Administration or per os in PEG-400 Solubilizer
CI-1041	6.6	5.3	
Co-101244	23	>20	5.9 mg/kg i.p.
EMD 95885	35	5.9	
CP-101.606	41	>20	58% effect at 20 mg/kg p.o. in PEG 400
Ro-256981	159	>20	5.1 mg/kg i.p.

Table 2 R0-binding and ED_{50} values of selected compounds

Example No.	ID Code of Compound	NDMA IC_{50} (μM)	Ro-Binding IC_{50} (μM)	Mouse Formalin Test	
				ED_{50} (mg/kg p.o.) in 5% Tween 80	ED_{50} (mg/kg p.o.) in 100% PEG 400
1	45 70001598	0.044	0.175	0.46	--
3	45 70001620	0.0032	0.0117	6.9	0.3
6	45 70001823	0.048	0.221	1.68	8.5
7	45 70001824	0.0014	0.0041	14.3	--
8	45 70001861	0.0024	0.0078	0.85	1.1
24	45 70001844	0.113	0.213	28.6	--
31	45 70002407	0.009	0.0398	4.4	7.1
35	45 70002480	0.0042	N.D.	1.98	--
41	45 70002724	0.099	N.D.	8.0	--
46	45 70002966	0.114	N.D.	10.8	--
59	45 70002339	0.048	0.0168	10.4	32
60	45 70002567	0.021	N.D.	--	6.2
61	45 70002567	0.013	0.0174	0.36	--
64	45 70002706	0.019	0.0168	0.17	--
67	45 70002739	0.014	0.132	--	5.7
101	45 70002346	0.011	0.0542	0.48	--
127	45 70002838	0.04	N.D.	1.80	--
142	45 70001655	0.017	0.0017	--	5.1
161	45 70002233	0.039	0.005	2.4	--

Applicants have therefore shown a predictable correlation between *in vitro* activity and the *in vivo* analgesic effect of the claimed compounds. A representative number of the claimed compounds show this analgesic effect, thereby enabling one of skill in the art to have a reasonable expectation of success in relieving pain using the claimed compounds, without undue experimentation.

Applicants believe that the rejection has been overcome, and respectfully request withdrawal of this rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete Reply has been made to the outstanding Office Action and, as such, the present Application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

Nancy J. Leith

Nancy J. Leith
Agent for Applicants
Registration No. 45,309

Date: March 23, 2007

6 W. Hubbard St.
Suite 500
Chicago, Illinois 60610
(312) 225-6342